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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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(54) **Title:** A NOVEL PROCESS FOR EZETIMIBE INTERMEDIATE

(57) **Abstract:** The invention provides a process for preparing intermediate of ezetimibe, which shows hypocholesterolemic activity. Thus 3-[5-(4-fluorophenyl)-1,5-dioxopentyl]-4-phenyl-2-oxazolidinone is reduced with (-)-DIP chloride to obtain 3-[(5S)-5-(4-fluorophenyl)-5-hydroxy-1-oxopentyl]-4-phenyl-2-oxazolidinone.

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A NOVEL PROCESS FOR EZETIMIBE INTERMEDIATE

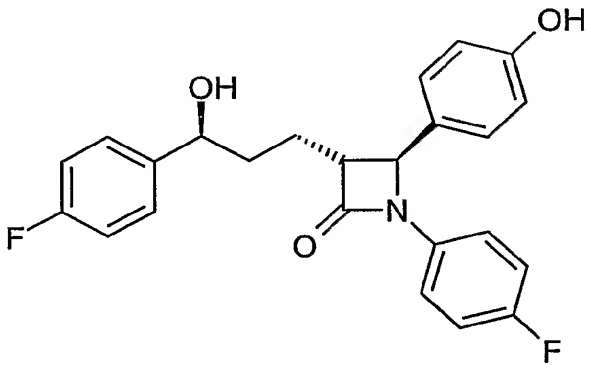
FIELD OF THE INVENTION

The present invention is related to a simple and economical process for the preparation of ezetimibe intermediate.

BACKGROUND OF THE INVENTION

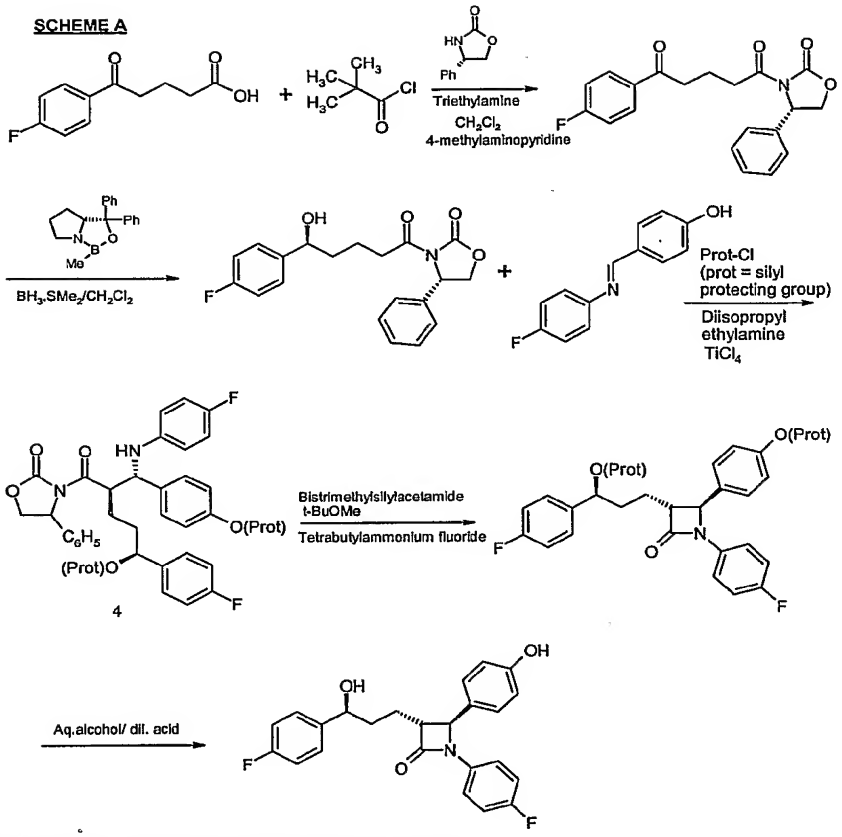
US 5,767,115 discloses the hypocholesterolemic activity of hydroxy-substituted azetidinones. Processes for preparing these compounds are described in US 5,767,115, WO 97/16424, WO 97/45406, US 5,886,171, WO 00/34240, J. Med. Chem. 1998, 41(6), 973-980 and J. Org. Chem. 1999, 64(10), 3714-18.

WO 00/34240 discloses an improved process for preparing these compounds, in particular ezetimibe, (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone of formula I.

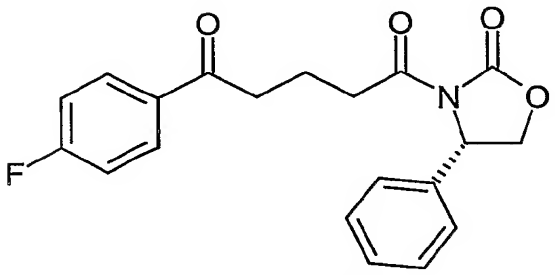


---------- I

The reaction sequence of process for preparing ezetimibe is shown in scheme A.

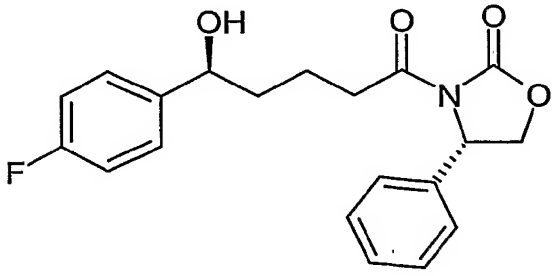


The reduction of the ketone of the formula 3a



---------- 3a

to give alcohol of formula 2a



---------- 2a

involves the use of the reducing agent borane dimethyl sulfide in the presence of the expensive chiral catalyst (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo(1,2-c)(1,3,2) oxaza-borolidine.

US Patent No. 5,618,707 describes microbial reduction of compound of formula 3a to form the compound of formula 2a. The process requires strict control of cultures and chromatographic separations, which make the process unsuitable for industrial production.

We have discovered that less expensive (-)-DIP chloride ((-)-β-chlorodiisopinocampheylborane) can be used for such asymmetric reductions, thereby avoiding the use of expensive twin reagents i.e. borane dimethyl sulfide and (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo(1,2-c)(1,3,2)oxaza-borolidine, and avoiding the 'difficult to handle' reagents.

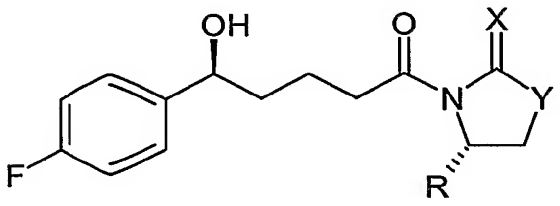
Thus the novel process is simple to handle and more economical than the known process.

The term lower alkyl refers to C1-C6 alkyl and the term lower alkoxy refers to C1-C6 alkoxy.

The object of the present invention is to provide a simple, cost effective process for the preparation of the ezetimibe intermediates.

SUMMARY OF THE INVENTION

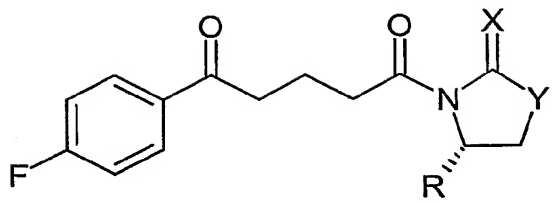
The present invention provides a process for preparing an alcohol of formula 2



---------- 2

wherein X is O or S; Y is O, S or N(lower alkyl); and R is alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl or lower alkoxy carbonyl, wherein substituents on phenyl and naphthyl are selected from the group consisting of lower alkyl and phenyl;

which comprises reducing the ketone of formula 3



---------- 3

wherein X-, Y- and R are as defined above, with (-)-DIP chloride ((-)-β-chlorodiisopinocampheylborane).

The compounds of formula 2 wherein X is O; Y is O; and R is alkyl, unsubstituted or substituted phenyl are the preferred.

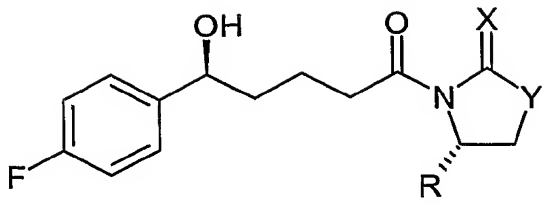
The reduction may be carried out in a neutral organic solvent or a combination of the neutral organic solvents. Neutral organic solvent means the solvent that is unreactive in the reduction reaction. The preferable neutral organic solvents are chloroalkanes such as methylene dichloride, chloroform, carbon tetrachloride and ethylene dichloride; carbocyclic aromatics such as toluene and benzene; ethers such as methyl tert-butyl ether, diethylether and isopropyl ether; heterocyclic compound such as tetrahydrofuran; dimethylformamide; dimethylsulfoxide; alkanes such as pentane and hexane; and acetonitrile. More preferable organic solvents are toluene, diethyl ether, isopropyl ether, hexane, methylene dichloride and ethylene dichloride.

Quantity of (-)-DIP chloride used is preferably at least about 0.3 mole, more preferably about 0.5 to 10 mole, most preferably about 0.8 to 5 mole per mole of the keto compound of formula 3.

The preferable reaction temperature is below the boiling temperature of the solvent used, more preferably between about –40°C and the boiling temperature of the solvent, still more preferably between about -20°C and 40°C and most preferably between about -10°C and 10°C.

DETAILED DESCRIPTION OF THE INVENTION

The compound of the formula 2



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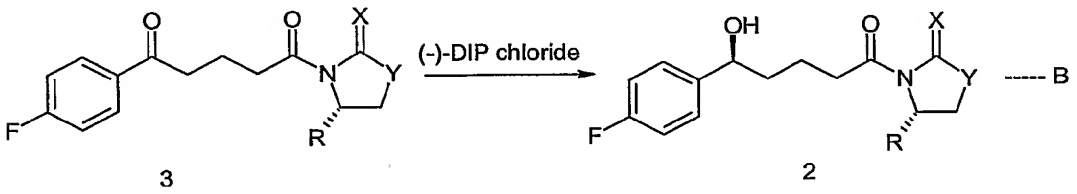
is an useful intermediate for the preparation of ezetimibe. The intermediates represented by the formula 2 can be prepared economically in good yields as represented by the scheme B.



3 2 ----- B

wherein X is O or S; Y is O, S or N(lower alkyl); and R is alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl or lower alkoxy carbonyl, wherein substituents on phenyl and naphthyl are selected from the group consisting of lower alkyl and phenyl.

The starting compounds of formula 3 are known or can be obtained from known methods.

The reduction may be carried out in a neutral organic solvent or a combination of the neutral organic solvents. Neutral organic solvent means the solvent that is unreactive in the reduction reaction. The preferable organic solvents are chloroalkanes such as methylene dichloride, chloroform, carbon tetrachloride and ethylene dichloride; carbocyclic aromatics such as toluene and benzene; ethers such as methyl tert-butyl ether, diethylether and isopropyl ether; heterocyclic compound such as tetrahydrofuran; dimethylformamide; dimethylsulfoxide; alkanes such as pentane and hexane; and acetonitrile. More preferable solvents are toluene, diethyl ether, isopropyl ether, hexane, methylene dichloride and ethylene dichloride.

The preferable reaction temperature is below the boiling temperature of the solvent used, more preferably between about –40°C and the boiling temperature of the solvent, still more preferably between about -20°C and 40°C and most preferably between about -10°C and 10°C.

Quantity of (-)-DIP chloride used is preferably at least about 0.3 mole, more preferably about 0.5 to 10 mole, most preferably about 0.8 to 5 mole per mole of the keto compound of formula 3.

Yield of the hydroxy compound of formula 2 is usually above 80%, typically between 90 % to 100%.

The compounds of formula 2 wherein X is O; Y is O; and R is alkyl, unsubstituted or substituted phenyl are the preferred.

Preferable conditions for obtaining a hydroxy compound of formula 2 from the corresponding keto compound of formula is that the keto compound of the formula 3 is mixed with a neutral solvent, reduced with (-)-DIP chloride at a temperature between –40°C and the boiling temperature of the solvent, more preferably between about -20°C and 40°C and most preferably between about -10°C and 10°C.

The reaction mass may be subjected to usual work up. The reaction mass may be used directly in the next step to produce finally ezetimibe, or the hydroxy compound may be isolated and used in the next step.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

Example 1

3-[5-(4-fluorophenyl)-1,5-dioxopentyl]-4-phenyl-2-oxazolidinone (100 gm) is dissolved in toluene (750 ml), the mixture of (-)-β-chlorodiisopinocampheylborane ((-)-DIP chloride) in heptane (545 ml, 1.5M) and toluene (750 ml) is added at 0^0C to 5^0C for 1 hour. The reaction mixture is stirred for 15 hours at 25^0C to 30^0C and 340 ml of 10% sodium chloride is then added at the same temperature. The layers are separated and the organic layer is washed with 5% sodium bicarbonate (300 ml), 1N sulfuric acid (300 ml), and 10% sodium chloride (300 ml). Then the organic layer is dried on sodium sulfate to give 3-[(5S)-5-(4-fluorophenyl)-5-hydroxy-1-oxopentyl]-4-phenyl-2-oxazolidinone in 96% yield.

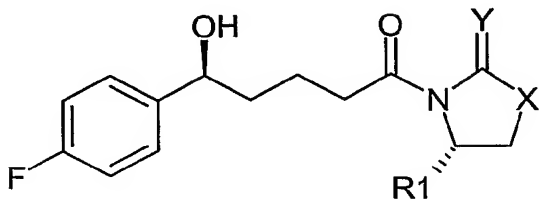
Example 2

The organic layer of 3-[(5S)-5-(4-fluorophenyl)-5-hydroxy-1-oxopentyl]-4-phenyl-2-oxazolidinone from example 1 is mixed with 4-fluoro-N-(4-hydroxyphenyl)methylene-benzenamine (121 gm) and cooled to -10^0C. Then

diisopropylethylamine (260 ml) is added to the reaction mixture for 45 minutes at –10^{0}C to -15^{0}C, trimethylsilylchloride (135 ml) is added and stirred for 1 hour at –20^{0}C to -25^{0}C. The reaction mixture is cooled to –30^{0}C, $TiCl_4$ (35 ml) is slowly added to the reaction mixture at –30^{0}C to -35^{0}C and stirred for 3 hours at the same temperature. 5% Aq. tartaric acid solution (1700 ml) is added to the reaction mixture at 0^{0}C, stirred for 1 hour and allowed the temperature to rise to 25^{0}C. Then 20% Aq. $NaHSO_3$ (350 ml) solution and stirred for 2 hours at 25^{0}C to 30^{0}C. The organic layer is separated and washed with 1000 ml water, concentrated to 250 ml volume and added 100 ml bistrimethylsilylacetamide. Then the reaction mixture is heated to reflux for 30 minutes. The organic layer is concentrated to remove methylene dichloride, crystallized from the mixture of ethyl acetate (250 ml) and n-heptane (250 ml), and filtered and dried to give 135 gm of compound 4 (prot = trimethylsilyl).

We claim:

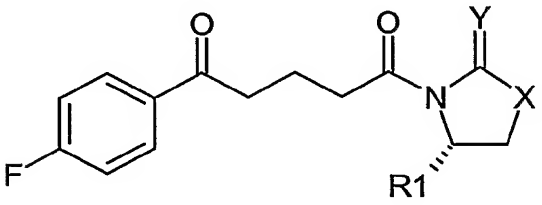
1) A process for the preparation of an alcohol of formula 2:



---------- 2

wherein X is O or S; Y is O, S or N(lower alkyl); and R is alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl or lower alkoxy carbonyl, wherein substituents on phenyl and naphthyl are selected from the group consisting of lower alkyl and phenyl;

which comprises reducing the ketone of formula 3:



---------- 3

wherein X-, Y- and R1 are as defined above, with (-)-DIP chloride ((-)-β-chlorodiisopinocampheylborane).

2) A process according to claim 1, wherein X is O; Y is O; and R is alkyl, unsubstituted or substituted phenyl.

3) A process according to claim 1, wherein the compound of the formula 2 is 3-[(5S)-5-(4-fluorophenyl)-5-hydroxy-1-oxopentyl]-4-phenyl-2-oxazolidinone.

4) A process according to claim 1, wherein the reduction is carried out in a neutral organic solvent or a combination of the organic solvents.

5) A process according to claim 4, wherein the organic solvent is selected from the group consisting of chloroalkanes such as methylene dichloride, chloroform, carbon tetrachloride and ethylene dichloride; carbocyclic aromatics such as toluene and benzene; ethers such as methyl tert-butyl ether, diethyl ether and isopropyl ether; heterocyclic compound such as

tetrahydrofuran; dimethylformamide; dimethylsulfoxide; alkanes such as pentane and hexane; and acetonitrile.

6) A process according to claim 4, wherein the organic solvent is selected from the group consisting of methylene dichloride, chloroform, carbon tetrachloride, ethylene dichloride, toluene, benzene, methyl tert-butyl ether, diethyl ether, isopropyl ether, tetrahydrofuran, dimethylformamide, dimethylsulfoxide, pentane, hexane and acetonitrile.

7) A process according to claim 6, wherein the organic solvent is selected from toluene, diethyl ether, isopropyl ether, hexane, methylene dichloride and ethylene dichloride.

8) A process according to claim 1, wherein the reaction is carried out below the boiling temperature of the solvent.

9) A process according to claim 8, wherein the reaction is carried out between about -20^0C and 40^0C.

10) A process according to claim 9, wherein the reaction is carried out between about -10^0C and 10^0C.

11) A process according to claim 1, wherein at least about 0.3 moles of (-)-DIP chloride per mole of the keto compound of formula 3 is used.

12) A process according to claim 11, wherein about 0.5 to 10 moles of (-)-DIP chloride per mole of the keto compound of formula 3 is used.

13) A process according to claim 13, wherein about 0.8 to 5 moles of (-)-DIP chloride per mole of the keto compound of formula 3 is used.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2003/000366

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 291/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT,Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: REG, CAPLUS, CASREACT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chandrasekharan, J.. Diisopinocampheylchloroborane, a remarkably efficient chiral reducing agent for aromatic prochiral ketones. Journal of Organic Chemistry (1995), 50 (25), 5446-8 (Eng.).Columbus Ohio USA: Chemical Abstracts, Vol.104,17 February 1986, page 700, the abstract No.69021r . *the whole abstract.*	1, 4-6, 8
X	Thompson, A.S. .Synthesis of PAF antagonist MK-287. Journal of Organic Chemistry (1992), 57 (26), 7044-52 (Eng.). Columbus Ohio USA: Chemical Abstracts, Vol.118, 1 February 1993, page 825 , the abstract No.59511a. *the whole abstract.*	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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„P" document published prior to the international filing date but later than the priority date claimed
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„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2004 (17.08.2004)	2 September 2004 (02.09.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer BÖHM K. Telephone No. 1/53424/519

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 03/00366-0

Patent document cited in search report	Publication date	Patent family member(s)	Publication date